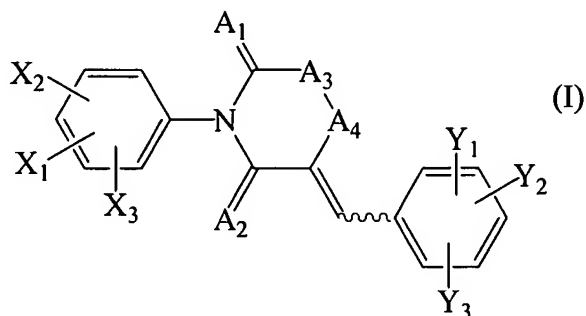


## Claims

1. A method of treating a subject having a cystic fibrosis transmembrane conductance regulator (CFTR) protein-mediated condition or symptom, the method comprising administering to the subject a therapeutically effective amount of a compound of formula (I):



wherein X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; A<sub>1</sub> and A<sub>2</sub> are independently chosen from oxygen and sulfur, A<sub>3</sub> is chosen from sulfur and selenium; and A<sub>4</sub> comprises one or more carbons or heteroatoms and may be present or absent; or a pharmaceutically acceptable derivative thereof, as an individual stereoisomer or a mixture thereof.

2. The method of claim 1, wherein the condition or symptom is associated with aberrantly increased intestinal secretion.

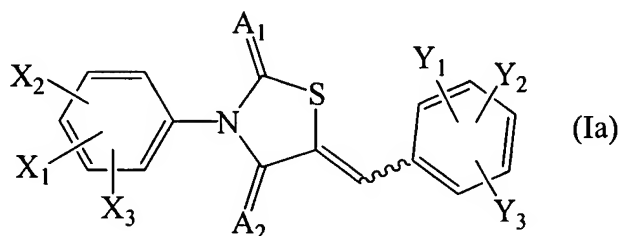
3. The method of claim 2, wherein the condition or symptom is secretory diarrhea.

4. The method of claim 1, wherein the compound of formula (I) is a compound where A<sub>4</sub> is absent, A<sub>1</sub> and A<sub>3</sub> are each sulfur, and A<sub>2</sub> is oxygen, *i.e.*, a 3-aryl-5-arylmethylene-2-thioxo-4-thiazolidinone.

5. The method of claim 1, wherein the compound of formula (I) is chosen from: 3-[(3-trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(4-oxycarboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-

trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,4-dihydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; and 3-[(3-trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone.

6. The method of claim 1, wherein the compound of formula (I) is a compound of formula (Ia):



wherein X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; and A<sub>1</sub> and A<sub>2</sub> are independently chosen from oxygen and sulfur.

7. The method of claim 6, wherein X<sub>1</sub> is an electron-withdrawing group.

8. The method of claim 7, wherein X<sub>1</sub> is selected from the group consisting of a perfluoroalkyl group and a fluoro group.

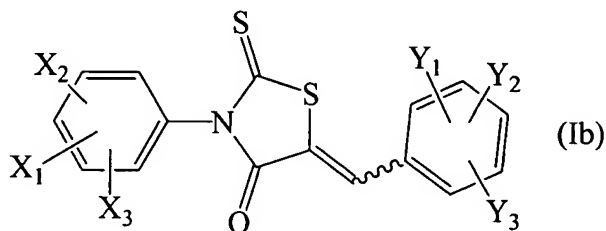
9. The method of claim 8, wherein Y<sub>2</sub> is chosen from alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and a halo group.

10. The method of claim 7, wherein X<sub>1</sub> is a 3-trifluoromethyl group.

11. The method of claim 6, wherein Y<sub>2</sub> is a hydroxyl group.

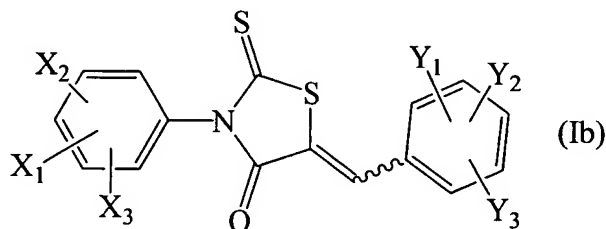
12. The method of claim 11, wherein Y<sub>1</sub> is a hydroxyl group.

13. The method of claim 11, wherein  $Y_1$  is a bromo group.
14. The method of claim 11, wherein  $Y_3$  is a nitro group.
15. The method of claim 1, wherein the compound of formula (I) is a compound of formula (Ib):



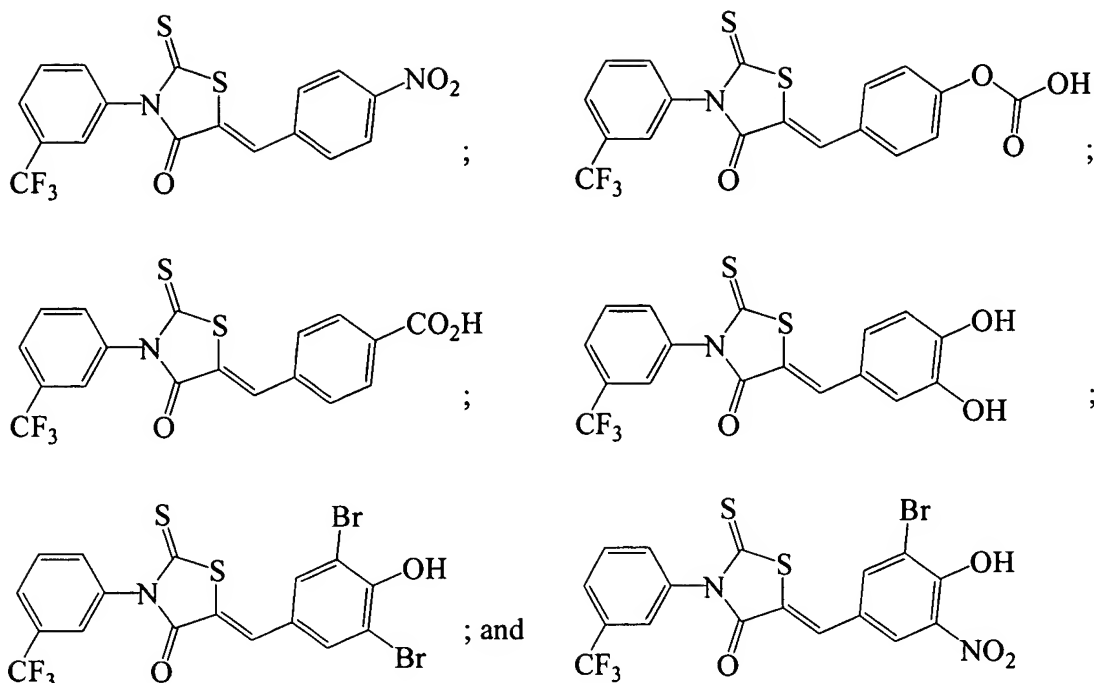
wherein  $X_1$ ,  $X_2$  and  $X_3$  are independently chosen from hydrogen and an organic group; and  $Y_1$ ,  $Y_2$  and  $Y_3$  are independently chosen from hydrogen and an organic group.

16. The method of claim 1, wherein the compound of formula (I) is a compound of formula (Ib):

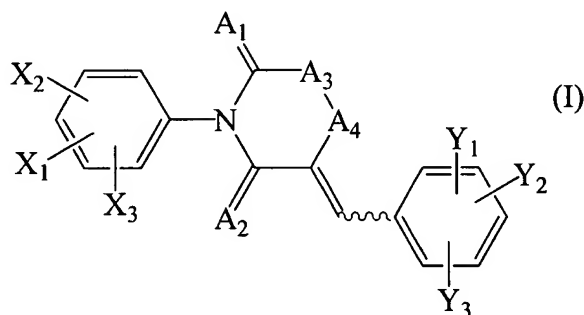


wherein at least one of  $X_1$ ,  $X_2$  and  $X_3$  is an electron-withdrawing group; and  $Y_1$ ,  $Y_2$  and  $Y_3$  are independently chosen from hydrogen, alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and a halo group.

17. The method of claim 16, wherein  $X_1$  is a trifluoromethyl group.
18. The method of claim 17, wherein  $X_1$  is a 3-trifluoromethyl group.
19. The method of claim 1, wherein the compound of formula (I) is chosen from:



20. A method for inhibiting the activity of cystic fibrosis transmembrane conductance regulator protein in a cell of a subject, comprising contacting the cell with a compound of formula (I):

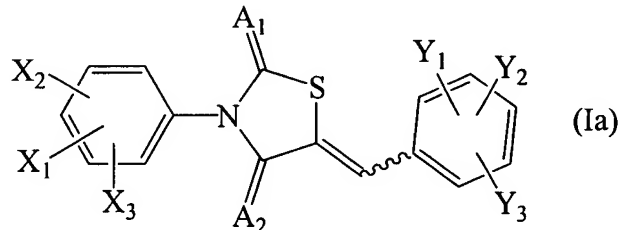


wherein  $X_1$ ,  $X_2$  and  $X_3$  are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group;  $Y_1$ ,  $Y_2$  and  $Y_3$  are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group;  $A_1$  and  $A_2$  are independently chosen from oxygen and sulfur,  $A_3$  is chosen from sulfur and selenium; and  $A_4$  comprises one or more carbons or heteroatoms and may be present or absent; or a pharmaceutically acceptable derivative thereof, as an individual stereoisomer or a mixture thereof; in an amount sufficient to inhibit CFTR ion transport in the cell.

21. The method of claim 20, wherein the compound of formula (I) is a compound where  $A_4$  is absent,  $A_1$  and  $A_3$  are each sulfur, and  $A_2$  is oxygen, *i.e.*, a 3-aryl-5-arylmethylene-2-thioxo-4-thiazolidinone.

22. The method of claim 21, wherein the compound of formula (I) is chosen from: 3-[(3-trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(4-oxycarboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,4-dihydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; and 3-[(3-trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone.

23. The method of claim 20, wherein the compound of formula (I) is a compound of formula (Ia):



wherein  $X_1$ ,  $X_2$  and  $X_3$  are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group;  $Y_1$ ,  $Y_2$  and  $Y_3$  are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; and  $A_1$  and  $A_2$  are independently chosen from oxygen and sulfur.

24. The method of claim 23, wherein  $X_1$  is an electron-withdrawing group.

25. The method of claim 24, wherein  $X_1$  is chosen from a perfluoroalkyl group and a fluoro group.

26. The method of claim 24, wherein  $X_1$  is a 3-trifluoromethyl group.

27. The method of claim 23, wherein  $Y_2$  is chosen from alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and halo groups.

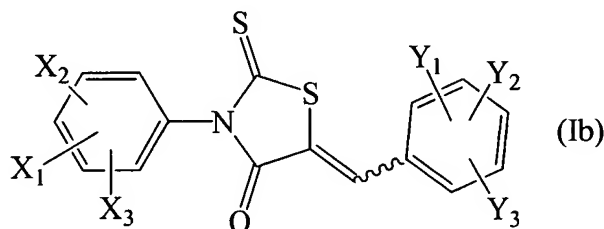
28. The method of claim 23, wherein  $Y_2$  is a hydroxyl group.

29. The method of claim 28, wherein  $Y_1$  is a hydroxyl group.

30. The method of claim 28 wherein  $Y_1$  is a bromo group.

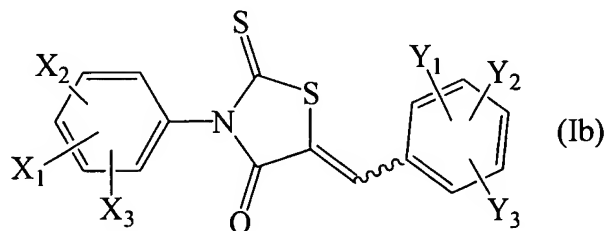
31. The method of claim 28, wherein  $Y_3$  is a nitro group.

32. The method of claim 20, the compound of formula (I) is a compound of formula (Ib):



wherein  $X_1$ ,  $X_2$  and  $X_3$  are independently chosen from hydrogen and an organic group; and  $Y_1$ ,  $Y_2$  and  $Y_3$  are independently chosen from hydrogen and an organic group.

33. The method of claim 20, wherein the compound of formula (I) is a compound of formula (Ib):

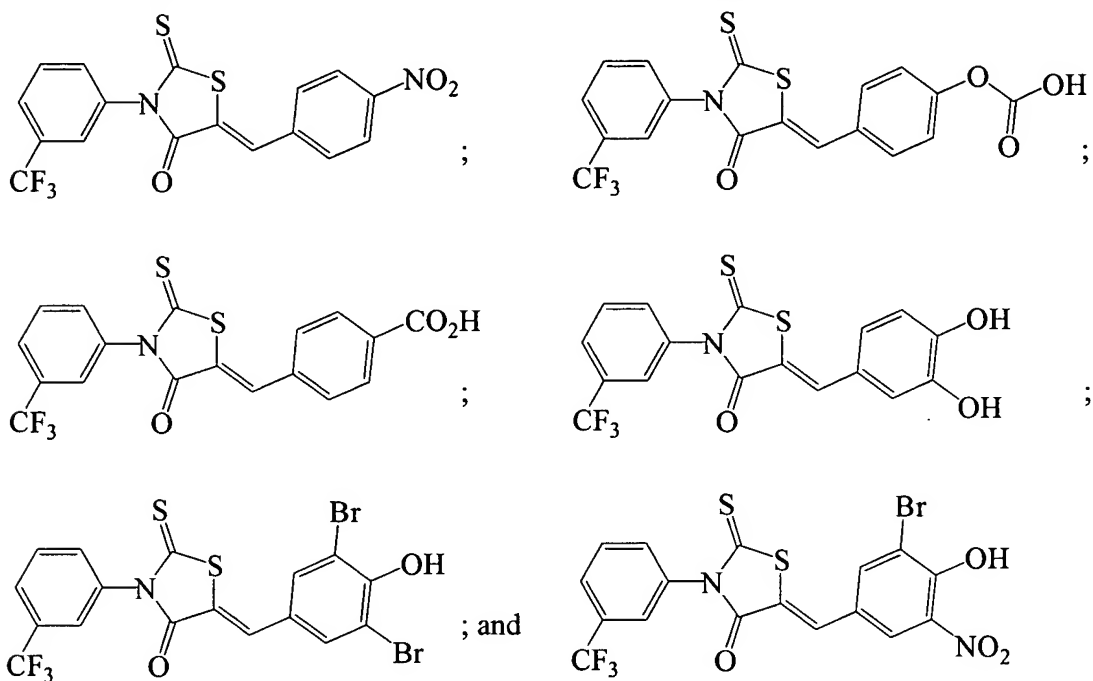


wherein at least one of  $X_1$ ,  $X_2$  and  $X_3$  is an electron-withdrawing group; and  $Y_1$ ,  $Y_2$  and  $Y_3$  are independently chosen from hydrogen, alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and a halo group.

34. The method of claim 33, wherein  $X_1$  is a trifluoromethyl group.

35. The method of claim 34, wherein  $X_1$  is a 3-trifluoromethyl group.

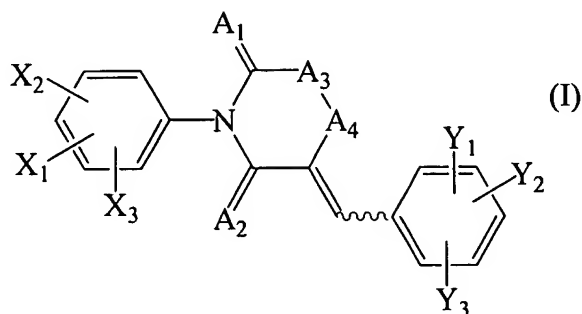
36. The method of claim 20, wherein the compound of formula (I) is chosen from:



37. The method of claim 20, wherein contacting the cell comprises ingesting, by the subject, the compound of formula (I).

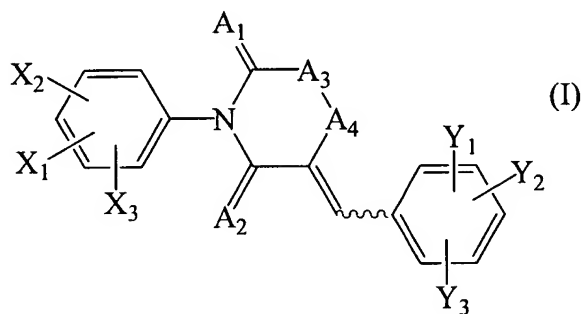
38. The method of claim 37, wherein the ingesting further comprises ingesting a pharmaceutically acceptable carrier together with the compound of formula (I).

39. A method for inhibiting the activity of cystic fibrosis transmembrane conductance regulator protein in a cell in an *in vivo* assay, comprising contacting the cell with a compound of formula (I):



wherein X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; A<sub>1</sub> and A<sub>2</sub> are independently chosen from oxygen and sulfur, A<sub>3</sub> is chosen from sulfur and selenium; and A<sub>4</sub> comprises one or more carbons or heteroatoms and may be present or absent; or a pharmaceutically acceptable derivative thereof, as an individual stereoisomer or a mixture thereof, in an amount sufficient to inhibit CFTR ion transport in the cell.

40. A method for producing the cystic fibrosis (CF) phenotype in a non-human animal, wherein the method comprises administering to the non-human animal a compound of formula (I):



wherein X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; A<sub>1</sub> and A<sub>2</sub> are independently chosen from



oxygen and sulfur, A<sub>3</sub> is chosen from sulfur and selenium; and A<sub>4</sub> comprises one or more carbons or heteroatoms and may be present or absent; or a pharmaceutically acceptable derivative thereof, as an individual stereoisomer or a mixture thereof; in an amount sufficient to induce the cystic fibrosis (CF) phenotype in the non-human animal.

41. A method of treating a subject having a condition associated with aberrant ion transport by cystic fibrosis transmembrane conductance regulator (CFTR) in a subject, the method comprising:

administering to the subject an efficacious amount of a thiazolidinone compound;  
wherein CFTR ion transport is inhibited and the condition is treated.

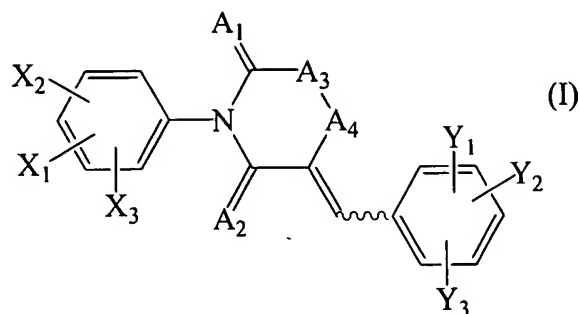
42. The method of claim 41, wherein the aberrantly increased CFTR ion transport is associated with diarrhea.

43. The method of claim 42, wherein the diarrhea is secretory diarrhea.

44. A pharmaceutical composition comprising a thiazolidinone compound , independently chosen from: 3-[(3-trifluoromethyl)phenyl]-5-[(4-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(4-oxycarboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(4-carboxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,4-dihydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; 3-[(3-trifluoromethyl)phenyl]-5-[(3,5-dibromo-4-hydroxyphenyl)methylene]-2-thioxo-4-thiazolidinone; and 3-[(3-trifluoromethyl)phenyl]-5-[(3-bromo-4-hydroxy-5-nitrophenyl)methylene]-2-thioxo-4-thiazolidinone; and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, a pharmaceutically acceptable excipient and a pharmaceutically acceptable adjuvant.

45. The composition of claim 44, wherein the composition does not contain detectable dimethyl sulfoxide.

46. A pharmaceutical composition comprising a compound of formula (I):

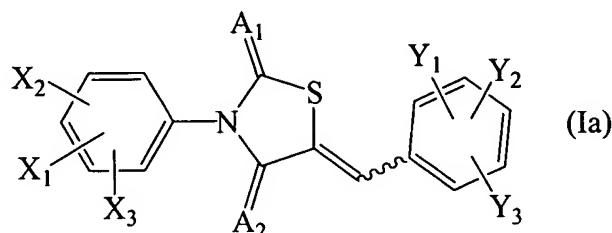


wherein  $X_1$ ,  $X_2$  and  $X_3$  are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group;  $Y_1$ ,  $Y_2$  and  $Y_3$  are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group;  $A_1$  and  $A_2$  are independently chosen from oxygen and sulfur,  $A_3$  is chosen from sulfur and selenium; and  $A_4$  comprises one or more carbons or heteroatoms and may be present or absent; or a pharmaceutically acceptable derivative thereof, as an individual stereoisomer or a mixture thereof, provided, however, that when:

- 1)  $A_4$  is absent,  $A_1$  and  $A_2$  are each oxygen,  $A_3$  is sulfur, one of  $X_1$ ,  $X_2$ , and  $X_3$  is trifluoromethyl or chloro in the 4-position and the others of  $X_1$ ,  $X_2$ , and  $X_3$  are each hydrogen, one of  $Y_1$ ,  $Y_2$ , and  $Y_3$  can not be 4-methylpiperazin-1-yl in the 2-position when the remaining others of  $Y_1$ ,  $Y_2$ , and  $Y_3$  are each hydrogen;
- 2)  $A_4$  is absent,  $A_1$  and  $A_3$  are each sulfur,  $A_2$  is oxygen, one of  $X_1$ ,  $X_2$ , and  $X_3$  is carboxyl in the 4-position and the others of  $X_1$ ,  $X_2$ , and  $X_3$  are each hydrogen,  $Y_1$ ,  $Y_2$ , and  $Y_3$  can not each be hydrogen;
- 3)  $A_4$  is absent,  $A_1$  and  $A_3$  are each sulfur,  $A_2$  is oxygen, one of  $X_1$ ,  $X_2$ , and  $X_3$  is hydroxy in the 2-, 3- or 4-position or ethoxy in the 4-position and the others of  $X_1$ ,  $X_2$ , and  $X_3$  are each hydrogen, one of  $Y_1$ ,  $Y_2$  and  $Y_3$  is hydrogen, and another of  $Y_1$ ,  $Y_2$  and  $Y_3$  is hydroxy or methoxy in the 4-position, the remaining one of  $Y_1$ ,  $Y_2$  and  $Y_3$  can not be methoxy in the 3-position; and
- 4)  $A_4$  is absent,  $A_1$  and  $A_3$  are each sulfur,  $A_2$  is oxygen, one of  $X_1$ ,  $X_2$ , and  $X_3$  is methyl in the 4-position and another of  $X_1$ ,  $X_2$ , and  $X_3$  is chloro in the 3-position, one of  $Y_1$ ,  $Y_2$  and  $Y_3$  is methoxy in the 4-position, the remaining others of  $Y_1$ ,  $Y_2$  and  $Y_3$  can not each be hydrogen;

and at least one of a pharmaceutically acceptable carrier, a pharmaceutically acceptable diluent, a pharmaceutically acceptable excipient and a pharmaceutically acceptable adjuvant.

47. The composition of claim 46, wherein the compound of formula (I) is a compound of formula (Ia):



wherein X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> are independently chosen from hydrogen, an organic group, a halo group, a nitro group, an azo group, a hydroxyl group and a mercapto group; and A<sub>1</sub> and A<sub>2</sub> are independently chosen from oxygen and sulfur.

48. The composition of claim 47, wherein X<sub>1</sub> is an electron-withdrawing group.

49. The composition of claim 48, wherein X<sub>1</sub> is chosen from a perfluoroalkyl group and a fluoro group.

50. The composition of claim 47, wherein Y<sub>2</sub> is chosen from alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and a halo group.

51. The composition of claim 47, wherein X<sub>1</sub> is a 3-trifluoromethyl group.

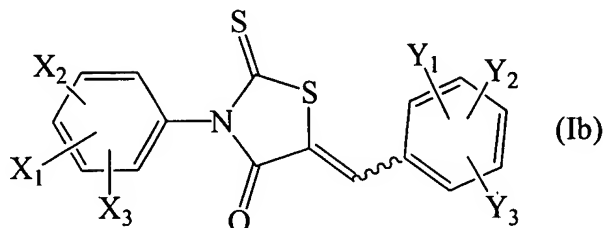
52. The composition of claim 47, wherein Y<sub>2</sub> is a hydroxyl group.

53. The composition of claim 52, wherein Y<sub>1</sub> is a hydroxyl group.

54. The composition of claim 52, wherein Y<sub>1</sub> is a bromo group.

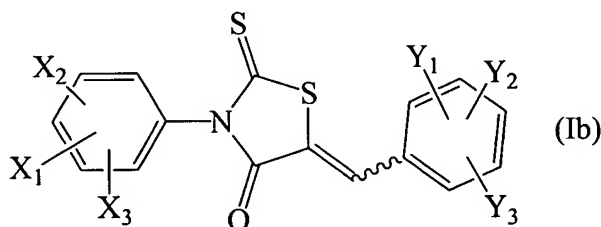
55. The composition of claim 54, wherein Y<sub>3</sub> is a nitro group.

56. The composition of claim 46, wherein the compound of formula (I) is a compound of formula (Ib):



wherein X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> are independently chosen from hydrogen and an organic group; and Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> are independently chosen from hydrogen and an organic group.

57. The composition of claim 46, wherein the compound of formula (I) is a compound of formula (Ib):



wherein at least one of X<sub>1</sub>, X<sub>2</sub> and X<sub>3</sub> is an electron-withdrawing group; and Y<sub>1</sub>, Y<sub>2</sub> and Y<sub>3</sub> are independently chosen from hydrogen, alkyl, hydroxyl, carboxyl, nitro, carbonate, carbamate, alkoxy, alkylcarbonyl, and a halo group.

58. The composition of claim 57, wherein X<sub>1</sub> is a trifluoromethyl group.

59. The composition of claim 57, wherein X<sub>1</sub> is a 3-trifluoromethyl group.

60. The composition of claim 46, wherein the composition does not contain detectable dimethyl sulfoxide.

61. A non-human animal having a cystic fibrosis transmembrane conductance regulator (CFTR) deficiency, wherein the deficiency is produced by administration of a thiazolidinone compound to the animal in an amount effective to inhibit CFTR ion transport.

62. The non-human animal of claim 61, wherein the animal is a mammal.

63. The non-human animal of claim 62, wherein the mammal is a non-human primate, rodent, ungulate, or avian.

64. The non-human animal of claim 61, wherein the animal has a phenotype similar to cystic fibrosis.